# Successful Umbilical Cord Blood Stem Cell Transplantation for Pelizaeus-Merzbacher Disease

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September 11, 2020

**Abstract**

Pelizaeus-Merzbacher Disease (PMD) is a rare X-linked recessive leukodystrophy caused by mutations in the proteolipid protein-1 gene on the Xq22.2 chromosome and is characterized clinically by nystagmus, spastic quadriplegia, ataxia and developmental delay. There is no definitive curative treatment. We report here a successful matched unrelated umbilical cord blood stem cell transplantation for PMD in a 2-year-old boy. He was conditioned with Busulfan, Cyclophosphamide and Rabbit anti-thymoglobulin. MMF and Cyclosporine were used as graft-vs-host disease prophylaxis. His neutrophil engrafted on day+29 and platelets on day+33. It lead to disease stabilisation and improvement in development of the child with PMD.

## Introduction

Pelizaeus-Merzbacher Disease (PMD) is a rare X-linked recessive leukodystrophy caused by mutations in the proteolipid protein-1 (PLP1) gene on the Xq22.2 chromosome (1,2). The primary biological deficiency in affected patients with PMD is the failure of oligodendrocytes to properly myelinate axons, resulting in axonal degeneration and neurological dysfunction (1). More than 50% of cases are caused by duplication of a genomic region, including the entire PLP1 gene (2,3). PMD is characterized clinically by nystagmus, spastic quadriplegia, ataxia, and developmental delay (1). There is no definitive curative treatment. We report here a successful matched unrelated umbilical cord blood stem cell transplantation (UCBT) for PMD in a 2-year-old boy.

## Methods

A 2-year-old Russian boy, first child of non-consanguineous parentage, presented to us with global developmental delay. Child had a history of prolonged seizures at $1\frac{1}{2}$ years of age and was symptomatically managed in his native country. Subsequently child had total 5 episodes of right sided focal seizures. On examination, he had hypotonia, unable to stand or walk, no speech and had developmental delay (developmental age was 10 months at 2-years of age) with no evidence of dysmorphism or neurocutaneous markers. Magnetic resonance imaging (MRI) of brain revealed symmetrical and widespread abnormality of the white matter of the cerebrum, brainstem, and cerebellum. Computerised tomography scan of head showed agenesis of corpus callosum & cerebellar vermis along with moderate ventriculomegaly. Genetic testing showed PLP-1 gene duplication confirming diagnosis of PMD. He then underwent an UCBT from a 10/10 matched unrelated cord at our centre. Parents gave written informed consent before transplant. Myeloablative conditioning was used with Busulfan day-9 to -6 (3.2mg/kg/day), Cyclophosphamide day-5 to -2 (50mg/kg/day), Rabbit anti-thymoglublin day-3 to -1 (2.5mg/kg/day) and Rituximab on day-8 (100mg/m2). Cord blood stem cell (CD34+) dose was 0.2 million/kg. Mycophenolate mofetil (MMF) and Cyclosporine were used as graft-vs-host disease (GVHD) prophylaxis.

## Results

His neutrophil engrafted on day+29 and platelets on day+33. Post-transplant on day+30 he had reactivation of Cytomegalovirus and BK virus along with haemorrhagic cystitis which was managed successfully. On day+53, he had an episode of hematemesis and melena with sudden drop in hemoglobin. Upper and lower gastrointestinal endoscopies were performed. Biopsies were suggestive of MMF induced enterocolitis which resolved after discontinuation of MMF. Chimerism on day+32, day+56 and day+100, 1-year and 2-years was fully donor. There was no evidence of acute or chronic GVHD. His further post-transplant period was uneventful. Neurodevelopmental assessment was done at 12 months and 24 months post-transplant which showed overall improvement in all domain of development. His motor skills improved, he can walk independently, run with infrequent falls and climb stairs. Child could speak in sentences play with blocks and follow instructions and had better social communications skills. No further seizures were recorded post-transplant. At present child is more than two years post-transplant and has developmental age of 3 years at 4 years of age. MRI of brain 24-months post UCBT has shown no change in myelination.

**Discussion**

In this report, we have described the clinical outcome of PMD after UCBT in a young boy. There was initial stabilization followed by improvement in neurological symptoms. There are mainly two clinical phenotypes of PMD - conatal and classic. Conatal PMD refers to the most severe form of the disease, with symptoms appearing at birth or within few weeks of life. These patients have severe stridor, seizures, hypotonia which later on develops to spasticity, dystonia and inability to walk or talk. The other form, classic PMD, is milder and presents with nystagmus at 2 to 6 months of age (1). Our patient although presented at 18-months of age but had severe symptoms -hypotonia, seizures and had developmental delay at presentation. MRI brain of PMD patients showed diffuse pattern of hypomyelination. Affected white matter regions include the cerebral hemispheres, cerebellum, and brainstem. Thinning of the corpus callosum and atrophy of the cerebral hemispheres is sometimes seen. Since this is a rare disease, formal natural history studies are lacking.

There are no curative treatments available. Various researchers have used different strategies. Although UCBT has been used to treat many inherited metabolic disorders but only recently, it has been investigated in PMD patients. Wishnew et al. demonstrated neurological improvement in two patients aged 9 months and 29 months respectively who underwent UCBT for PMD in their centre. With 7-year and 1-year follow-up, they showed stabilization of disease with significant gains in cognitive skills and modest gains in motor development along with stable engraftment. MRI results also suggested interval myelination in these patients (4). Our patient is now more than 24-months post UCBT and has shown overall good improvement in all domain of development. Child can walk, speak, play and follow instructions. No further seizures were recorded post-transplant. Post-transplant MRI in our case has not shown much change in myelination.

Gupta et al. reported a 1-year open-label phase 1 study undertaken to evaluate safety and to detect evidence of myelin formation after human central nervous system stem cells (HuCNS-SC) transplantation. Allogeneic HuCNS-SCs were surgically implanted into the frontal lobe white matter in four male subjects with an early-onset severe form of PMD. Modest gains in neurological function were observed in three of the four subjects (5). Further follow up of these 4 children for another 4-years has been reported recently. At year 2, all subjects exhibited diffusion MRI changes at the implantation sites as well as in more distant brain regions. There were persistent, increased signal changes in the three patients who were studied up to year 5. Two of four subjects developed donor-specific HLA alloantibodies, demonstrating that neural stem cells can elicit an immune response when injected into the CNS (6). Osorio et al. reviewed the use of various stem cells in the treatment of PMD without any breakthrough success (7). Our case has achieved better developmental milestones as compared to all the reported cases in literature; 2 post UCBT and 4 post HuCNS-SC who had minimal to modest improvement. In conclusion, UCBT lead to disease stabilisation and improvement in development of the child with PMD. Long-term follow up of our case is needed.

**Disclosure** – All authors have nothing to declare

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